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Journal Pre-proof

Number of initial symptoms is more related to long COVID-19 than acute severity of infection: a prospective cohort of hospitalized patients.

Chan Sui Ko Adrien , Candellier Alexandre , Mercier Marie , Joseph Cédric , Jean-Luc Schmit , Lanoix Jean-Philippe , Andrejak Claire

HIGHLIGHTS

- Long COVID-19 was experienced by almost two thirds of hospitalized patients.

- High number of initial symptoms increases the risk of long covid.

- Objective measures of COVID-19 severity are unable to predict long COVID-19.

- Hypertension and female sex are also associated with persistent symptoms.

- Patients with a high number of initial symptoms should be closely monitored.

Number of initial symptoms is more related to long COVID-19 than acute severity of infection: a prospective cohort of hospitalized patients.

Chan Sui Ko Adrien[1], Candellier Alexandre[2], Mercier Marie[3], Joseph Cédric[1], Jean-Luc Schmit[1] Lanoix Jean-Philippe[1], Andrejak Claire[3].

1. Department of Infectious Diseases, Centre Hospitalier Universitaire Amiens-Picardie, Amiens, 80054 France

2. Department of Nephrology, Centre Hospitalier Universitaire Amiens-Picardie, Amiens 80054 France

3. Department of Pneumology, Centre Hospitalier Universitaire Amiens-Picardie, Amiens 80054 France

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Corresponding author:

Chan Sui Ko Adrien,

Department of Infectious Disease,

Centre Hospitalier Universitaire Amiens-Picardie,

80054 Amiens,

France

Email: chansuiko.adrien@chu-amiens.fr

Introduction

Post-COVID-19 symptoms experienced by many survivors after infection have a further devastating effect. Reports of risk factor of long COVID-19 are rising but data including reliable assessment of persistent symptoms by structured face to face follow up visit are scarce (Halpinet al. 2021). Here we report a study assessing post-COVID-19 associated risk factors in hospitalized patients including those requiring ICU four months after admission. We provide also data about objective measures of COVID-19 severity e.g., oxygen requirement, inflammatory biomarkers and radiological findings.

Methods

We conducted a prospective cohort study of hospitalized patients with COVID-19, discharged from the Amiens Picardie University Hospital, France, from 2nd February 2020 to 28th December 2020. SARS-CoV-2 infection was confirmed by polymerase chain reaction (PCR) in nasopharyngeal swab. Clinical, biological, radiological and hospitalization data were collected from hospital medical records. All patients were assessed by trained physicians during a face-to-face structured follow-up visits and asked about a list of post-COVID symptoms. Clinical examination, blood analysis and lung CT-scan was also performed during this dedicated visit. Long Covid was considered in patients exhibited post-COVID persistent symptoms 4 months after the hospital admission. Multivariable adjusted logistic regression models were constructed to identify clinical and hospitalization variables associated with post-COVID-19 syndrome in a stepwise manner and Poisson regression to identify those associated with the number of persistent symptoms. All tests were two-sided, and a p-value less than 0.05 was considered statistically significant. For this study we used data from SEQCOV cohort, the study protocol was approved by institutional review board and CHU Amiens-Picardie ethics committee (PI2018_843_0049).

Results

From 586 discharged patients, a total of 316 patients achieved a four-month structured follow up visit. Patients with follow up evaluation conducted in other hospital or declined (n=138), died (n=34) or with missing data (n=98) were excluded. Two hundred and one (63.6%) of patients had at least one symptom at the follow-up.

The demographic and clinical characteristics of participants are shown in Table 1. Overall, the mean age was 64 years, with 187 (59%) men. The prevalence of hypertension was higher in patients with long COVID, other comorbidities were not different for the two groups. Both patient groups had similar oxygen therapy requirement, admission to ICU, inflammatory markers, and CT-scan abnormalities. Patients reported 5 (IQR: 3-6) symptoms at the admission. Hyperthermia (79.1%), cough (70.6%), dyspnea (68%), myalgia (50.6%) were mainly reported. Participants were assessed a median of 115 days after hospital discharge. The most frequent persistent symptoms were dyspnea (39.2%) and asthenia (37.1%). Distribution of symptoms is shown figure 1.

In univariate analysis, women had significantly increased risk (OR = 1.89 95% CI [1.16-3.03], p=0.01) than men. Patient with hypertension (OR = 1.64 95% CI [1.04-2.61], p=0.04) experienced persistent symptoms more frequently. The number of initial symptoms (OR = 1.27 95% CI [1.12-1.45], p<0.001) or patient with five or more initial symptoms showed greater risk for long-COVID-19 (OR = 2.47 95%CI [1.12-3.03]).

In multivariate logistic regression, female sex (OR = 1.94 95% CI [1.17-3.22], p=0.01) hypertension (OR = 2.01 95% CI [1.22-3.31], p<0.01) and the number of initial symptoms (OR = 1.35 95% CI [1.17-1.54], p<0.001) remained significantly associated with persistent symptoms (supplementary Table 1). Similarly, in multivariate Poisson regression, the number of persistent symptoms was significatively associated with the number of initial symptoms

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(adjusted incidence rate ratios, aIRR = 1.16 95% CI [1.11-1.22], p<0.001) as well as female sex (aIRR = 1.56 95% CI [1.29-1.87], p<0.001), hypertension (aIRR = 1.23 95% CI [1.02-1.50], p=0.03) and length of stay in hospital (aIRR = 1.01 95% CI [1.005-1.017], p<0.001)

Discussion

In our prospective cohort study, female sex, hypertension, and high number of initial symptoms increased the risk of long covid, and the number of persistent symptoms independently of acute disease severity and clinical course in hospitalized patients.

Our study is in line with reports suggesting that the prevalence of long covid is higher in women compared with men (Bai etal. 2021; Blomberg et al. 2021; Carvalho et al. 2021; Huang et al. 2020; Munblit et al. 2021; Wynberg et al. 2021). After detailed analysis of comorbidities we showed that hypertension was the most significant risk factor for long COVID-19. Number of initial symptoms had already been described as risk factor of persistent symptoms, in ambulatory (Sudre et al. 2021), and in hospitalized patient (Fernández-de-Las-Peñas et al. 2021; Peghin et al. 2021), results that are confirmed here in this large prospective cohort. Interestingly, severity of acute COVID-19 infection evaluated by oxygen requirement, inflammatory response, or CT-scan findings was not associated with persistent symptoms. Our study suggest that long-term burden of COVID-19 involve multiple non-respiratory symptoms, and was not associated with acute severity or related post-intensive care syndrome. Strengths of this study are the completeness of data including objective markers of disease severity and reliable symptoms collection by face-to-face interview during medical assessment. Our study included sufficient severe forms of COVID-19 with more than a third of ICU admission's cases, and infectious or thrombotic complications. This study has several limitations: first, only hospitalized patient alive at follow up were analysed and we might not have captured enough discharged patients;

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second, we performed follow-up visits in a single university center, results might not reflect

all hospitalized patient.

Identification of risk factors associated with long COVID could be used to target early

intervention and developments to support rehabilitation.

Ethical Approval:

This Research was approved by the Ethics Review committee of the CHU AMIENS-Picardie.

Declaration of Competing Interest:

The authors declare no conflict of interest

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None

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Table 1: Demographic and clinical characteristics of enrolled patients according to persistent COVID symptoms.
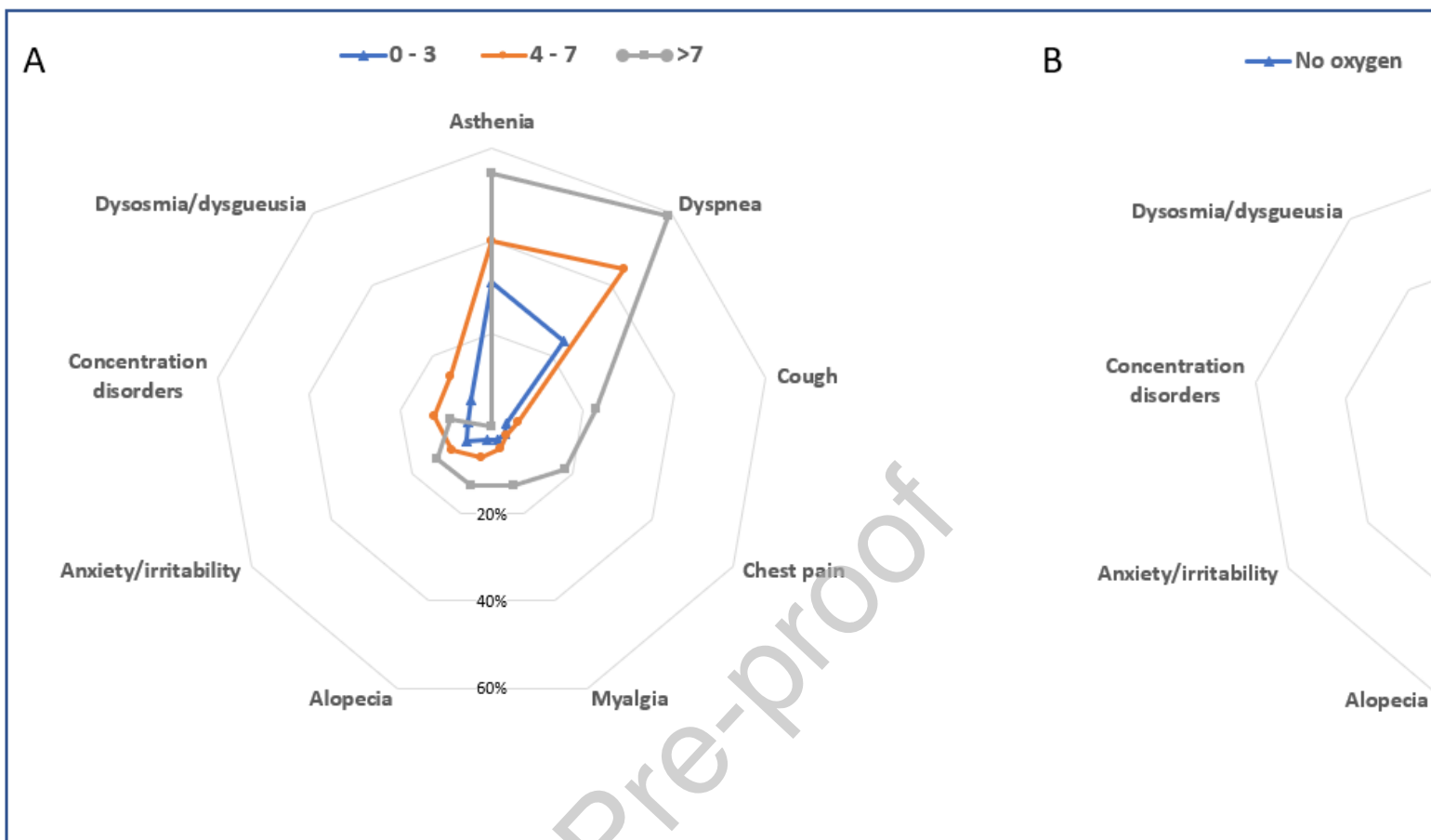
Figure1: **Prevalence of persistent symptoms.**
A: Distribution of persistent symptoms according to the number of initial symptoms (0 - 3: n=96; 4 - 7: n=198; >7: n=22)
B: Distribution of persistent symptoms according to the severity of acute COVID-19 (no oxygen: n=39; ward patients: n= 135 pat

	Overall (n=316)	No persistent symptoms (n=115)	Persistent symptoms (n=201)	p-value
Characteristics				
Age (years)	64.1 ± 14.3	64.7 ± 13.7	63.8 ± 14.7	0.62
>65 years old	156 (49.4)	60 (52.2)	96 (47.8)	0.45
Female	129 (40.8)	36 (31.3)	93(46.3)	0.01
Body Mass Index (kg/m²)	30.27 ± 6.6	29.9 ± 7.0	30.4 ± 6.2	0.45
Obesity >30 kg/m²	147 (47)	48 (42.5)	99 (49.5)	0.23
Comorbidities				
Hypertension	165 (52.2)	51 (44.3)	114 (56.7)	0.03

Diabetes	85 (26.9)	34 (29.6)	51 (25.4)	0.42
Smoking	119 (37.7)	48 (41.7)	71 (35.3)	0.28
Chronic cardiovascular disease	97 (30.7)	38 (30.0)	59 (29.4)	0.49
Chronic lung disease	68 (21.5)	26 (22.6)	42 (20.9)	0.72
Chronic kidney failure	17 (5.4)	7 (6.1)	10 (5.0)	0.67
Neoplasia	12 (3.8)	5 (4.3)	7 (3.5)	0.70
Other (pregnancy, hepatic or neurologic diseases, immunocompromised)	57 (18.0)	15 (13.0)	42 (20.9)	0.11
Number of comorbidities	2 (1-3)	2 (0-3)	2 (1-3)	0.62
0	67 (21.2)	30 (26.1)	37 (18.4)	0.27
1 or 2	134 (42.4)	46 (40)	88 (43.8)	-
3 or more	115 (36.4)	39 (33.9)	76 (37.8)	-
Chronic treatments				
Corticosteroids	17 (5.4)	6 (5.2)	11 (5.5)	0.92
Immunosuppressive therapy	21 (6.6)	11 (9.6)	10 (5.0)	0.12
ACE inhibitors	68 (21.5)	29 (25.2)	39 (19.4)	0.23
ARB	41 (13)	11 (9.6)	30 (14.9)	0.17
Beta-blocker	66 (20.9)	20 (17.4)	46 (22.9)	0.25
Metformin	50 (15.8)	21 (18.3)	29 (14.4)	0.37
Disease severity				
Numbers of initial symptoms	5 (3-6)	4 (3-5)	5 (4-6)	0.006
0-4	145 (45.9)	69 (60)	50 (24.9)	<0.001
5 or more	171 (54.1)	46 (40)	151 (75.1)	<0.001
ICU admission	115 (36.4)	41 (35.7)	74 (36.8)	0.84
Oxygen requirement				
None	39 (12.3)	17 (14.8)	22 (10.9)	0.38
O2<4l/min	135 (42.7)	47 (40.9)	88 (43.8)	0.57
O2>4l/min	50 (15.8)	22 (19.0)	28 (12.4)	0.23
HFNC or NIV	38 (12.0)	16 (13.7)	22 (10.9)	0.45
IMV	53 (16.8)	13 (11.3)	40 (19.9)	0.05
Laboratory results				
Nadir lymphocyte (/mm^3)	804 ± 385	795 ± 395	814 ± 379	0.68
Lymphopenia <750/mm^3	158 (50.9)	63 (55.3)	95 (48.5)	0.25
CRP max (mg/L)	140 ± 94	139 ± 94	142 ± 96	0.76

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CRP > 150mg/L	122 (39.1)	44 (38.9)	78 (39.2)	0.96
Lung parenchymal involvement at CT-scan				0.46
No parenchymal abnormalities	18 (7.1)	10 (10.4)	8 (5.1)	
<25%	95 (37.5)	34 (35.4)	61 (38.9)	
25-50%	81 (32.0)	30 (31.3)	51 (32.5)	
>50%	59 (23.3)	22 (22.9)	37 (23.6)	
Clinical course				
Length of stay in hospital in days (IIQ)	10 (6-19)	11 (6-16)	10 (6-21)	0.84
1-6	88 (27.8)	35 (30.4)	53 (26.4)	0.44
7 or more	228 (72.2)	80 (69.6)	148 (73.3)	-
Infectious complications	57 (18)	17 (14.8)	40 (19.9)	0.26
Thrombotic complications	23 (7.3)	8 (7.0)	15 (7.5)	0.87
Follow-up				
Time from symptom onset to follow up in days,	121 (109-139)	121 (110-137)	120 (109-140)	0.78
Time from hospitalization admission to follow up (days)	115 (103-130)	115 (104-130)	114 (102-131)	0.48
Persisting symptoms:				
Asthenia	121 (38.3)		121 (60.2)	
Myalgia	16 (5.1)		16 (8)	
Chest pain	14 (4.4)		14 (7.0)	
Cough	19 (6.0)		19 (9.5)	
Dyspnea	124 (39.2)		124 (61.7)	
Anosmia/dysosmia	20 (6.3)		20 (10.0)	
Agueusia/dysgeusia	15 (4.7)		15 (7.5)	
Headache	7 (2.2)		7 (3.5)	
Concentration disorder	32 (10.1)		32 (15.9)	
Anxiety/irritability	29 (9.2)		29 (14.4)	
Alopecia	20 (6.3)		20 (10.0)	
Lung parenchymal involvement at CT-scan ¤				0.33
No parenchymal abnormalities	122 (40.7)	48 (43.2)	74 (39.2)	
<25%	127 (42.4)	47 (42.3)	80 (42.3	
25-50%	42 (14.0)	15 (13.5)	27 (14.3)	

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>50%	9 (3.0)	1 (0.9)	8 (4.2)	
HAD-A score	6.7 ± 4.3	4.7 ± 3.4	7.5 ± 4.3	<0.001
HAD-D score	5.2 ± 5.1	2.8 ± 3.5	6.4 ± 5.4	<0.001

Abbreviations are: ACE: Angiotensin Convertase Enzyme; ARB: angiotensin II Receptor Blocker, ICU: Intensive Care Unit, CRP: C-reactive protein, HNFC: High Flow Nasal Cannula for oxygen therapy, IMV: invasive mechanical ventilation. ¤: 300 patients. HAD: Hospital Anxiety and Depression Scale a subscale score (A or D) ≥11 denotes anxiety or depression

Quantitative variables are presented as mean ±standard deviation or median (interquartile Range), categorical variables are presented as absolute numbers (percentages).